

A Comparison of Bimolecular Reaction Models for Stochastic Reaction Diffusion Systems

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Abstract

Stochastic reaction-diffusion models have become an important tool in studying how both noise in the chemical reaction process and the spatial movement of molecules influences the behavior of biological systems. There are two primary spatially-continuous models that have been used in recent studies; the diffusion limited reaction model of Smoluchowski, and a second approach popularized by Doi. Both models treat molecules as points undergoing Brownian motion. The former represents chemical reactions between two reactants through the use of reactive boundary conditions, with two molecules reacting instantly upon reaching a fixed separation (called the reaction-radius). The Doi model uses reaction potentials, whereby two molecules react with a fixed probability per unit time, λ , when separated by less than the reaction radius. In this work we study the rigorous relationship between the two models. For the special case of a protein diffusing to a fixed DNA binding site, we prove that the solution to the Doi model converges to the solution of the Smoluchowski model as $\lambda \rightarrow \infty$, with a rigorous $O(\lambda^{-\frac{1}{2}+\epsilon})$ error bound (for any fixed $\epsilon > 0$). We investigate by numerical simulation, for biologically relevant parameter values, the difference between the solutions and associated reaction time statistics of the two models. As the reaction-radius is decreased, for sufficiently large but fixed values of λ , these differences are found to increase like the inverse of the binding radius.

1 Introduction

Stochastic reaction-diffusion models have become a popular tool for modeling biological systems in which both noise in the chemical reaction process and the spatial diffusion of molecules play an important roll. Such models have been used in a multitude of recent studies, examining the dynamics of synaptic transmission [33]; the MinCDE system in bacteria [10]; how proteins search for DNA binding sites [26]; and studies of signaling in the cell membrane [9]. There are three primary stochastic reaction-diffusion models that these studies have made use of; the diffusion limited reaction model of Smoluchowski [35, 28], what we call the Doi model [38, 5, 6], and the reaction diffusion master equation (RDME) [16, 12, 27].

In the Doi and Smoluchowski models, the positions of molecules are represented as points undergoing Brownian motion. Bimolecular reactions between two molecules in the Doi model occur with a fixed probability per unit time when two reactants are separated by *less* than some specified “reaction radius”. The Smoluchowski model differs by representing bimolecular reactions in one of two ways; either occurring instantaneously, or with fixed probability per unit time, when two reactants’ separation is *exactly* the reaction-radius [35, 28]. In this work we focus on the former case (often called a pure absorption reaction). For both models unimolecular reactions represent internal processes. They are assumed to occur with exponentially distributed times

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based on a specified reaction-rate constant. For general chemical systems, both the Doi and Smoluchowski models can be described by, possibly infinite, systems of partial integral differential equations (PIDEs) for the probability densities of having a given number of each chemical species and the corresponding locations of each molecule.

The RDME is spatially discrete, and given by a, possibly infinite, system of ODEs for the numbers of each chemical species located at each lattice site. It can be interpreted as an extension of the non-spatial chemical master equation (CME) [16, 32, 15, 39] model for stochastic chemical kinetics. *Formally*, the RDME has been shown to be an approximation to both the Doi model [22] and the Smoluchowski model [23, 25, 13, 20] for appropriately chosen lattice spacings. These approximations break down for systems involving bimolecular reactions, in two or more dimensions, *in the limit* that the lattice spacing approaches zero [23, 20]. (Recently we have suggested a new convergent RDME (CRDME) that converges to the Doi model as the lattice spacing is taken to zero [24].)

There are a plethora of numerical methods and simulation packages that have been developed to study biological systems based on one of the Smoluchowski, Doi, or RDME models. These include the λ - ρ method [11, 31], the CRDME [24], the FPKMC [7, 36], MCELL [29], MesoRD [14], Smoldyn [1], STEPS [21], and URDME [8]. While these numerical methods and software packages have been used in many modeling efforts, it is still an open question how exactly the underlying mathematical models they approximate are rigorously related. Moreover, to compare the results of modeling studies it would be helpful to understand how to choose parameters in the Doi (resp. Smoluchowski) model to accurately approximate the Smoluchowski (resp. Doi) model.

To address these questions, we investigate the rigorous relationship between the Doi and (pure absorption) Smoluchowski models. We begin in the next section by giving a brief overview of the general Doi and Smoluchowski models for the bimolecular reaction $A + B \rightarrow C$. (The two models are identical for systems with only first or zeroth order reactions.) We then consider the special case of a single protein searching for a DNA binding site within the nucleus of a eukaryotic cell in Section 3. The binding site is located at the origin, and the nucleus is modeled as a concentric sphere of radius R . With the further assumption that the initial distribution of the protein’s position is rotationally invariant, the Doi and Smoluchowski models can be simplified to spherically-symmetric diffusion equations. For the Doi model the diffusing protein is allowed to bind with probability per unit time λ when within a reaction-radius, r_b , of the binding site. This leads to a “reaction potential” in the PDE for the Doi model. In the Smoluchowski model the protein reacts instantly upon reaching a separation r_b from the binding site. This leads to the replacement of the reaction potential with a zero Dirichlet boundary condition on the sphere of radius r_b around the origin.

Denote by $p_\lambda(r, t)$ the spherically symmetric probability density that the diffusing molecule is r from the origin at time t in the Doi model, and by $\rho(r, t)$ the corresponding probability density in the Smoluchowski model. In Section 4 we numerically calculate the difference between $p_\lambda(r, t)$ and $\rho(r, t)$ for biologically relevant parameter values. We find that $p_\lambda(r, t) \rightarrow \rho(r, t)$ uniformly in r and t as $\lambda \rightarrow \infty$, with an empirical convergence rate that is $O(\lambda^{-\frac{1}{2}})$. The same empirical convergence rate is observed for the corresponding binding time distributions and mean binding times of the two models. For sufficiently large, but fixed, values of λ , as r_b is decreased the difference between the probability densities, binding time distributions, and mean binding times increase like r_b^{-1} .

These results motivate our studies in Section 5, where we rigorously prove the convergence of $p_\lambda(r, t)$ to $\rho(r, t)$ as $\lambda \rightarrow \infty$ with an $O(\lambda^{-\frac{1}{2}+\epsilon})$ error bound (for all $\epsilon > 0$). Let μ_n denote the n th eigenvalue of the generator of the Doi model (see (15)), with α_n the n th eigenvalue of the generator of the Smoluchowski model (see (11)). Our approach is to first prove that for λ sufficiently large, if $\alpha_n \leq M(\lambda)$ with $M(\lambda)$ a specified increasing function of λ , then

$$|\alpha_n - \mu_n| \leq \frac{C}{\lambda^{\frac{1}{2}-\epsilon}}$$

for any fixed $\epsilon > 0$. The precise statement of this result is given in Theorem 5.1. This theorem is then

used to show the corresponding eigenfunction convergence result in Lemma 5.1. Denote by $\psi_n(r)$ the n th eigenfunction of the generator of the Doi model (15), and $\phi_n(r)$ the corresponding eigenfunction of the Smoluchowski model (11). We prove for λ sufficiently large and $\mu_n < M(\lambda)$ that

$$\sup_{r \in [r_b, R]} |\phi_n(r) - \psi_n(r)| \leq \frac{C}{\lambda^{\frac{1}{2}-\epsilon}}.$$

Finally, the preceding two results are used to prove that

$$\sup_{t \in (\delta, \infty)} \sup_{r \in (r_b, R)} |p_\lambda(r, t) - \rho(r, t)| \leq \frac{C}{\lambda^{\frac{1}{2}-\epsilon}}, \quad (1)$$

for any $\epsilon > 0$ and $\delta > 0$ fixed. The precise statement of this result is given in Theorem 5.2.

It should be noted that the approximation of Dirichlet boundary conditions by reaction potentials is a well-studied problem in the context of the large-coupling limit in quantum physics [19]. Our approach of proving convergence through successive eigenvalue, eigenfunction, and PDE solution estimates differs from the more standard resolvent and path integral estimates [37, 3, 2]. A similar convergence rate of the Doi model solution to the Smoluchowski model solution was proven in $L^2(\mathbb{R}^3)$ in [4] (as opposed to the uniform convergence rate (1) we prove in a spherical domain). Denote by $\mathbf{1}_{[0, r_b]}(r)$ the indicator function of the interval, $[0, r_b]$. Convergence rates for eigenvalues of the general one-dimensional operator $-\frac{d^2}{dx^2} + V(x) + \lambda W(x)$ as $\lambda \rightarrow \infty$, for $x \in \mathbb{R}$, were proven in [17]. In contrast, in Section 5 we study the spherically symmetric operator arising in the Doi model, $-\frac{d^2}{dr^2} - \frac{2}{r} \frac{d}{dr} + \lambda \mathbf{1}_{[0, r_b]}(r)$ for $r \in [0, R]$ with a Neumann boundary condition at R , directly.

2 General Doi and Smoluchowski Models

We first illustrate how the bimolecular reaction $A + B \rightarrow C$ would be described by the Doi and Smoluchowski models in \mathbb{R}^3 . In the Doi model, bimolecular reactions are characterized by two parameters; the separation at which molecules may begin to react, r_b , and the probability per unit time the molecules react when within this separation, λ . In the Doi and Smoluchowski models, when a molecule of species A and a molecule of species B react we assume the C molecule they produce is placed midway between them.

We now formulate the Doi model as an infinite coupled system of PIDEs. Let $\mathbf{q}_l^a \in \mathbb{R}^3$ denote the position of the l th molecule of species A when the total number of molecules of species A is a . The state vector of the species A molecules is then given by $\mathbf{q}^a = (\mathbf{q}_1^a, \dots, \mathbf{q}_a^a) \in \mathbb{R}^{3a}$. Define \mathbf{q}^b and \mathbf{q}^c similarly. We denote by $f^{(a,b,c)}(\mathbf{q}^a, \mathbf{q}^b, \mathbf{q}^c, t)$ the probability density for there to be a molecules of species A, b molecules of species B, and c molecules of species C at time t located at the positions \mathbf{q}^a , \mathbf{q}^b , and \mathbf{q}^c . Molecules of the same species are assumed indistinguishable. In the Doi model the evolution of $f^{(a,b,c)}$ is given by

$$\frac{\partial f^{(a,b,c)}}{\partial t}(\mathbf{q}^a, \mathbf{q}^b, \mathbf{q}^c, t) = (L + R) f^{(a,b,c)}(\mathbf{q}^a, \mathbf{q}^b, \mathbf{q}^c, t). \quad (2)$$

Note, with the subsequent definitions of the operators L and R this will give a coupled system of PIDEs over all possible values of (a, b, c) . More general systems that allow unbounded production of certain species would result in an infinite number of coupled PIDEs. The diffusion operator, L , is defined by

$$L f^{(a,b,c)}(\mathbf{q}^a, \mathbf{q}^b, \mathbf{q}^c, t) = \left(D^A \sum_{l=1}^a \Delta_l^a + D^B \sum_{m=1}^b \Delta_m^b + D^C \sum_{n=1}^c \Delta_n^c \right) f^{(a,b,c)}(\mathbf{q}^a, \mathbf{q}^b, \mathbf{q}^c, t), \quad (3)$$

where Δ_l^a denotes the Laplacian in the coordinate \mathbf{q}_l^a and D^A the diffusion constant of species A. D^B , D^C , Δ_m^b , and Δ_n^c are defined similarly.

To define the reaction operator, R , we must introduce notations to represent removing or adding a specific molecule to the state \mathbf{q}^a . Let

$$\mathbf{q}^a \setminus \mathbf{q}_l^a = (\mathbf{q}_1^a, \dots, \mathbf{q}_{l-1}^a, \mathbf{q}_{l+1}^a, \dots, \mathbf{q}_a^a), \quad \mathbf{q}^a \cup \mathbf{q} = (\mathbf{q}_1^a, \dots, \mathbf{q}_a^a, \mathbf{q}).$$

$\mathbf{q}^a \setminus \mathbf{q}$ will denote \mathbf{q}^a with any one component with the value \mathbf{q} removed. Denote by $\mathbf{1}_{[r \leq r_b]}(r)$ the indicator function of the interval $[0, r_b]$, and let $B_l^c = \{\mathbf{q} \in \mathbb{R}^3 \mid |\mathbf{q} - \mathbf{q}_l^c| \leq r_b/2\}$ label the set of points a reactant could be at to produce a molecule of species C at \mathbf{q}_l^c . The Doi reaction operator, R , is then

$$(Rf^{(a,b,c)})(\mathbf{q}^a, \mathbf{q}^b, \mathbf{q}^c, t) = \lambda \left[\sum_{l=1}^c \int_{\mathbf{q} \in B_l^c} f^{(a+1,b+1,c-1)}(\mathbf{q}^a \cup \mathbf{q}, \mathbf{q}^b \cup (2\mathbf{q}_l^c - \mathbf{q}), \mathbf{q}^c \setminus \mathbf{q}_l^c, t) dB_l^c \right. \\ \left. - \sum_{l=1}^a \sum_{l'=1}^b \mathbf{1}_{[0, r_b]}(|\mathbf{q}_l^a - \mathbf{q}_{l'}^b|) f^{(a,b,c)}(\mathbf{q}^a, \mathbf{q}^b, \mathbf{q}^c, t) \right]. \quad (4)$$

In the Fock space representation of [5, 6], the term $Rf^{(a,b,c)}$ is called a reaction potential [6].

The Smoluchowski model would modify (2) by adding a reactive boundary condition and changing the reaction operator (4). The reactive boundary condition, often called a “pure absorption” boundary condition, is the Dirichlet boundary condition that

$$f^{(a,b,c)}(\mathbf{q}^a, \mathbf{q}^b, \mathbf{q}^c, t) = 0, \quad \text{if } |\mathbf{q}_l^a - \mathbf{q}_m^b| = r_b, \text{ for any } l, m. \quad (5)$$

We define by $S_l^c = \{\mathbf{q} \in \mathbb{R}^3 \mid |\mathbf{q} - \mathbf{q}_l^c| = r_b/2\}$ the set of points reactants could be at to produce a molecule of species C at \mathbf{q}_l^c . For $\mathbf{q} \in S_l^c$, denote by $J_l^{(a+1,b+1,c-1)}(\mathbf{q}^a \cup \mathbf{q}, \mathbf{q}^b \cup (2\mathbf{q}_l^c - \mathbf{q}), \mathbf{q}^c \setminus \mathbf{q}_l^c, t)$ the diffusive flux along the inward normal to the surface S_l^c from $f^{(a+1,b+1,c-1)}(\mathbf{q}^a \cup \mathbf{q}, \mathbf{q}^b \cup (2\mathbf{q}_l^c - \mathbf{q}), \mathbf{q}^c \setminus \mathbf{q}_l^c, t)$, immediately prior to a reaction producing \mathbf{q}_l^c . The reaction-operator, R , is then

$$(Rf^{(a,b,c)})(\mathbf{q}^a, \mathbf{q}^b, \mathbf{q}^c, t) = \sum_{l=1}^c \int_{\mathbf{q} \in S_l^c} J_l^{(a+1,b+1,c-1)}(\mathbf{q}^a \cup \mathbf{q}, \mathbf{q}^b \cup (2\mathbf{q}_l^c - \mathbf{q}), \mathbf{q}^c \setminus \mathbf{q}_l^c, t) dS_l^c. \quad (6)$$

Note, in the Smoluchowski model if the molecules are instead assumed to react with some fixed probability per unit time upon collision, a “partial absorption” Robin boundary condition would be used, see [28, 13]. We do not consider this more general reaction mechanism in this work.

3 Diffusion of a Protein to a Fixed DNA Binding Site

To study the rigorous relationship between the Doi and Smoluchowski models we investigate the special case of the chemical reaction $A + B \rightarrow \emptyset$, with only one molecule of species A and one molecule of species B. We further assume the molecule of species B is located at the origin and stationary ($D^B = 0$). The molecule of species A is assumed to move within a sphere of radius R centered on the B molecule. We denote the diffusion constant of the A molecule by D and the reaction radius by r_b . While idealized, this special case can be interpreted as a model for the diffusion of a DNA binding protein to a fixed DNA binding site (located at the center of a nucleus).

We now formulate the Doi and Smoluchowski models in this special case, with the additional assumption of spherical symmetry. This assumption will hold whenever the initial distribution of the A molecule is spherically-symmetric about the origin. Denote by $\rho(r, t)$ the spherically-symmetric probability density that the A molecule is a distance r from the origin and has not reacted with the B molecule at time t . Then the Smoluchowski model (2), (3), (5), (6) reduces to

$$\frac{\partial \rho}{\partial t} = D \Delta_r \rho, \quad r_b < r < R, t > 0, \quad (7)$$

where Δ_r denotes the spherically symmetric Laplacian in three-dimensions,

$$\Delta_r \equiv \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial}{\partial r} \right).$$

This equation is coupled with the reactive Dirichlet boundary condition, and zero Neumann boundary condition (so that the molecule remains in the “nucleus”)

$$\rho(r_b, t) = 0, \quad \frac{\partial \rho}{\partial r}(R, t) = 0, \quad t > 0.$$

Finally, we denote by $g(r)$ the initial condition, $\rho(r, 0) = g(r)$, with the normalization $\int_{r_b}^R g(r) r^2 dr = 1$.

Let $p_\lambda(r, t)$ label the corresponding spherically-symmetric probability density for the Doi model. In the special case we are considering, the PIDEs for the Doi model (2), (3), (4) reduce to

$$\frac{\partial p_\lambda}{\partial t} = D \Delta_r p_\lambda - \lambda \mathbf{1}_{[0, r_b]}(r) p_\lambda(r, t), \quad 0 \leq r < R, \quad t > 0, \quad (8)$$

with the Neumann boundary condition,

$$\frac{\partial p_\lambda}{\partial r}(R, t) = 0, \quad t > 0,$$

and the initial condition that

$$p_\lambda(r, 0) = \tilde{g}(r) = \begin{cases} g(r), & r > r_b, \\ 0, & r \leq r_b. \end{cases}$$

For simplicity, in what follows, we assume $D = 1$. Equations (7) and (8) can be solved explicitly by separating variables. In solving (8) we impose continuity of the function and its derivative across the surface of discontinuity as justified by the results of [18] and [34]. The computations are standard so we give only the final results. Denote by $(u(r), v(r)) = \int_0^R u(r)v(r)r^2 dr$ the usual L^2 inner product. We can then write the solutions as

$$\rho(r, t) = \sum_{n=1}^{\infty} a_n (\tilde{g}(r), \phi_n(r)) \phi_n(r) e^{-\alpha_n t} \quad (9)$$

and

$$p_\lambda(r, t) = \sum_{n=1}^{\infty} b_n (\tilde{g}(r), \psi_n(r)) \psi_n(r) e^{-\mu_n(\lambda)t}. \quad (10)$$

Here

$$\phi_n(r) = \frac{1}{r} \left[\frac{\sin(\sqrt{\alpha_n}(R-r))}{R\sqrt{\alpha_n}} - \cos(\sqrt{\alpha_n}(R-r)) \right], \quad r_b < r < R$$

are the eigenfunctions for the Smoluchowski model (7), satisfying

$$-\Delta_r \phi_n(r) = \alpha_n \phi_n(r), \quad r_b < r < R, \quad (11)$$

with the boundary conditions $\phi_n(r_b) = 0$ and $\frac{\partial \phi_n}{\partial r}(R) = 0$. We extend these functions to $[0, R]$ by defining $\phi_n(r) = 0$ for $r \in [0, r_b]$. The corresponding eigenvalues, α_n , solve the equation $f(\alpha_n) = 0$, where

$$f(\mu) = \frac{R\sqrt{\mu} - \tan(\sqrt{\mu}(R-r_b))}{R\mu \tan(\sqrt{\mu}(R-r_b)) + \sqrt{\mu}}. \quad (12)$$

The eigenfunctions for the Doi model (8) are given by

$$\psi_n(r) = \begin{cases} \psi_n^{in}(r), & 0 < r < r_b, \\ \psi_n^{out}(r), & r_b \leq r < R, \end{cases}$$

where

$$\psi_n^{in}(r) = \begin{cases} \frac{\frac{1}{R\sqrt{\mu_n}} \sin(\sqrt{\mu_n}(R - r_b)) - \cos(\sqrt{\mu_n}(R - r_b))}{\sinh(r_b\sqrt{\lambda - \mu_n})} \left(\frac{\sinh(r\sqrt{\lambda - \mu_n})}{r} \right), & \mu_n < \lambda, \\ \frac{\frac{1}{R\sqrt{\mu_n}} \sin(\sqrt{\mu_n}(R - r_b)) - \cos(\sqrt{\mu_n}(R - r_b))}{\sin(r_b\sqrt{\mu_n - \lambda})} \left(\frac{\sin(r\sqrt{\mu_n - \lambda})}{r} \right), & \mu_n > \lambda, \end{cases} \quad (13)$$

and

$$\psi_n^{out}(r) = \frac{1}{r} \left[\frac{\sin(\sqrt{\mu_n}(R - r))}{R\sqrt{\mu_n}} - \cos(\sqrt{\mu_n}(R - r)) \right]. \quad (14)$$

They satisfy the equation

$$-\Delta_r \psi_n(r) + \lambda \mathbf{1}_{[0, r_b]} \psi_n(r) = \mu_n \psi_n(r), \quad 0 \leq r < R, \quad (15)$$

with the Neumann boundary condition $\frac{\partial \psi_n}{\partial r}(R) = 0$.

The Doi eigenvalues, μ_n , solve the equation $f(\mu_n) = A(\mu_n, \lambda)$ with

$$A(\mu, \lambda) = \begin{cases} \sqrt{\frac{1}{\lambda - \mu}} \tanh(\sqrt{\lambda - \mu} r_b), & \mu < \lambda, \\ \sqrt{\frac{1}{\mu - \lambda}} \tan(\sqrt{\mu - \lambda} r_b), & \mu > \lambda. \end{cases} \quad (16)$$

We denote the dependence of the eigenvalues on λ by $\mu_n(\lambda)$. The constants a_n and b_n are given by

$$a_n = \frac{1}{(\phi_n(r), \phi_n(r))}, \quad b_n = \frac{1}{(\psi_n(r), \psi_n(r))}.$$

4 Difference Between Smoluchowski and Doi Models for Biologically Relevant Parameters

If we interpret (7) and (8) as models for the diffusion of a protein that has just entered the nucleus ($r_0 = R$) to a DNA binding site, then typically r_b would be between .1 and 10 nm [30, 9, 1], R between 1 and 10 μm , and D between 1 and 20 $\mu m^2 s^{-1}$. In the following we assume that all spatial units are in micrometers and time is in seconds, with $R = r_0 = 1 \mu m$, $D = 10 \mu m^2 s^{-1}$, and λ having units of s^{-1} . We also assume that $p_\lambda(r, 0) = \rho(r, 0) = \delta(r - r_0)/4\pi r^2$. p_λ and ρ are then the same as in the previous section, but rescaled by $(4\pi)^{-1}$.

We numerically evaluated $p_\lambda(r, t)$ and $\rho(r, t)$ in MATLAB using the eigenfunction expansions (10) and (9). The series were truncated at the first term with magnitude smaller than 10^{-10} . In evaluating these series numerically it is necessary to calculate a number of the eigenvalues μ_n and α_n . For each term of the eigenfunction expansions the transcendental equations for the corresponding Doi eigenvalue, $f(\mu_n) = A(\mu_n, \lambda)$, and the Smoluchowski eigenvalue, $f(\alpha_n) = 0$, were solved to 25 digits of precision using the Mathematica `Reduce` function. In Figure 1a we show the solution to the Smoluchowski model (7), $\rho(r, t)$, when $r_b = 10^{-3} \mu m$. For short times the solution is localized near R , while a boundary layer develops near $r = r_b$ as t increases. Figure 1b shows the maximum absolute difference between p_λ and ρ for a discrete set of points,

$$\|p_\lambda(r, t) - \rho(r, t)\|_\infty \equiv \sup_i \sup_j |p_\lambda(r_i, t_j) - \rho(r_i, t_j)|,$$

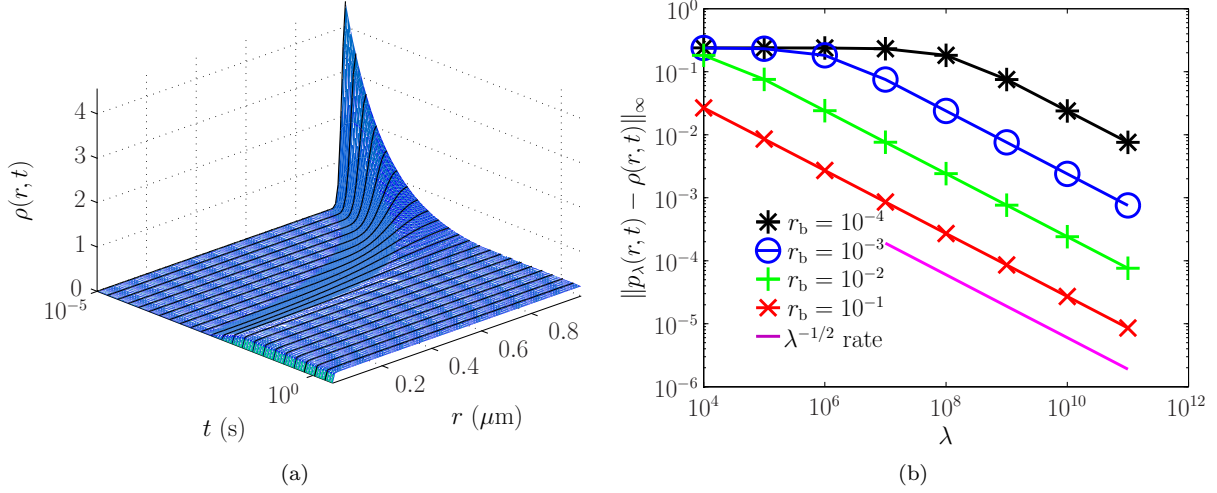


Figure 1: (a) Solution to the Smoluchowski model (7) for $r_b = 10^{-3}\mu\text{m}$. Note that the t -axis uses a logarithmic scale. (b) Absolute difference in $p_\lambda(r, t)$ and $\rho(r, t)$ as λ and r_b are varied.

where r_i and t_j are given in Appendix B by Listings 1 and 2. For each fixed value of r_b we see that as $\lambda \rightarrow \infty$ the difference between p_λ and ρ converges to zero like $\lambda^{-1/2}$. As r_b is decreased, the absolute difference increases by approximately an order of magnitude for each fixed value of λ (for λ sufficiently large).

For many biological models the statistics of the random variable, for the time at which the diffusing molecule first binds to the binding site, are of interest. For example, in [26] we studied how this time was influenced by volume exclusion due to the spatially varying density of chromatin inside the nucleus of mammalian cells. We subsequently denote these random variables by T_{Doi} and T_{Smol} . Statistics of these random variables can be calculated from the cumulative distribution functions

$$\text{Prob}[T_{\text{Doi}} < t] = 1 - 4\pi \int_0^R p_\lambda(r, t) r^2 dr,$$

and

$$\text{Prob}[T_{\text{Smol}} < t] = 1 - 4\pi \int_{r_b}^R \rho(r, t) r^2 dr.$$

We evaluated $\text{Prob}[T_{\text{Doi}} < t]$ and $\text{Prob}[T_{\text{Smol}} < t]$ by analytically integrating the eigenfunction expansions (10) and (9) and evaluating the truncated series in MATLAB. (Using the same method as described above for evaluating $p_\lambda(r, t)$ and $\rho(r, t)$.)

Figure 2a shows $\text{Prob}[T_{\text{Smol}} < t]$ for varying r_b and demonstrates a constant increase in the binding time as r_b is decreased (on a logarithmic scale). Figure 2b shows the absolute difference in binding time distributions,

$$\|\text{Prob}[T_{\text{Doi}} < t] - \text{Prob}[T_{\text{Smol}} < t]\|_\infty \equiv \sup_{t_j} |\text{Prob}[T_{\text{Doi}} < t_j] - \text{Prob}[T_{\text{Smol}} < t_j]|,$$

where t_j is given by Listing 2 in Appendix B. We again observe an empirical $\lambda^{-1/2}$ convergence rate of $\text{Prob}[T_{\text{Doi}} < t]$ to $\text{Prob}[T_{\text{Smol}} < t]$ as $\lambda \rightarrow \infty$. For a biologically relevant binding radius of $10^{-3}\mu\text{m}$, when $\lambda = 10^{11}\text{s}^{-1}$ the absolute difference between the two distributions is on the order of 10^{-3} .

In addition to the probability densities and binding time distributions, we also examined the mean time for the diffusing protein to find the binding site (when starting a distance r_0 from the origin). The mean binding

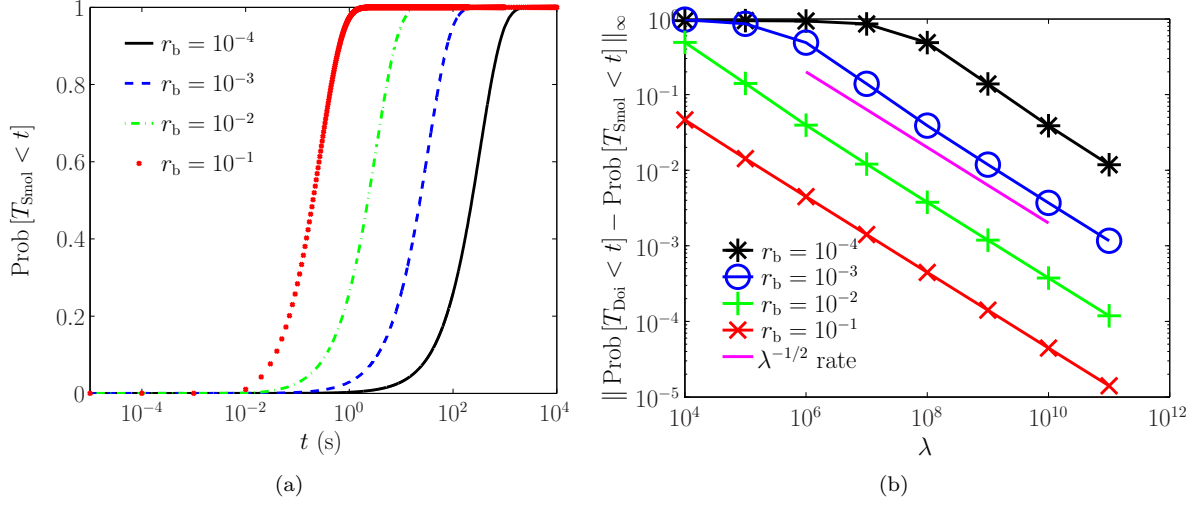


Figure 2: (a) Smoluchowski binding time distributions for varying r_b . Note the t -axis is logarithmic. (b) Absolute difference in binding time distributions from the Smoluchowski and Doi models as λ is varied.

time for the Doi model can be found in a simple closed form by solving the corresponding mean first passage time problem (29), see Appendix A, and is given by

$$\mathbb{E}[T_{\text{Doi}}](r_0) = \int_0^\infty \text{Prob}[T_{\text{Doi}} < t] dt = \begin{cases} u^-(r_0), & r_0 < r_b, \\ u^+(r_0), & r_0 > r_b. \end{cases} \quad (17)$$

Where, for $\hat{\lambda} = \lambda/D$, we have that

$$u^-(r_0) = \frac{1}{D\hat{\lambda}} + \left(\frac{\sinh(\sqrt{\hat{\lambda}}r_0)}{r_0} \right) \left[\frac{R^3 - r_b^3}{3D(r_b\sqrt{\hat{\lambda}}\cosh(\sqrt{\hat{\lambda}}r_b) - \sinh(\sqrt{\hat{\lambda}}r_b))} \right],$$

$$u^+(r_0) = \frac{r_b^2 - r_0^2}{6D} + \frac{R^3}{3D} \left[\frac{1}{r_b} - \frac{1}{r_0} \right] + \frac{1}{D\hat{\lambda}} + \left(\frac{\sinh(\sqrt{\hat{\lambda}}r_b)}{r_b} \right) \left[\frac{R^3 - r_b^3}{3D(r_b\sqrt{\hat{\lambda}}\cosh(\sqrt{\hat{\lambda}}r_b) - \sinh(\sqrt{\hat{\lambda}}r_b))} \right].$$

Similarly, the mean binding time in the Smoluchowski model can be found by solving the mean first passage time problem (30), and is given by

$$\mathbb{E}[T_{\text{Smol}}](r_0) = \frac{r_b^2 - r_0^2}{6D} + \frac{R^3}{3D} \left[\frac{1}{r_b} - \frac{1}{r_0} \right], \quad r_0 > r_b. \quad (18)$$

Figure 3a shows the mean binding time in the Doi model as λ is varied for $r_0 = R$.

The difference between the two mean binding times, for $r_0 > r_b$, is then given by

$$|\mathbb{E}[T_{\text{Doi}}](r_0) - \mathbb{E}[T_{\text{Smol}}](r_0)| = \left| \frac{1}{D\hat{\lambda}} + \left(\frac{\sinh(\sqrt{\hat{\lambda}}r_b)}{r_b} \right) \left[\frac{R^3 - r_b^3}{3D(r_b\sqrt{\hat{\lambda}}\cosh(\sqrt{\hat{\lambda}}r_b) - \sinh(\sqrt{\hat{\lambda}}r_b))} \right] \right|. \quad (19)$$

This difference is $O(\lambda^{-\frac{1}{2}})$, consistent with the results we prove in the next section on the uniform convergence of p_λ to ρ as $\lambda \rightarrow \infty$. (19) also demonstrates that for large, but fixed values of λ the absolute difference in

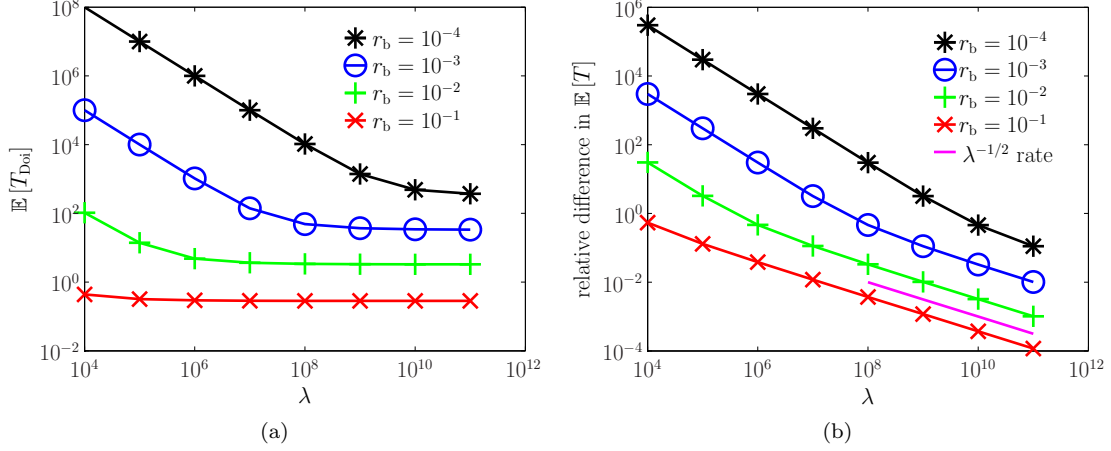


Figure 3: (a) Mean binding time of Doi model vs λ . (b) Relative difference in mean binding times (20).

mean binding times will increase like r_b^{-1} as r_b is decreased. In Figure 3b the relative difference,

$$\frac{|\mathbb{E}[T_{\text{Smol}}] - \mathbb{E}[T_{\text{Doi}}]|}{\mathbb{E}[T_{\text{Smol}}]}, \quad (20)$$

is graphed as λ is varied for $r_0 = R$, illustrating the $\lambda^{-1/2}$ convergence of $\mathbb{E}[T_{\text{Doi}}]$ to $\mathbb{E}[T_{\text{Smol}}]$. For $r_b = 10^{-3} \mu\text{m}$ the mean binding times differ by less than 1% when $\lambda = 10^{11} \text{ s}^{-1}$.

Each of Figures 1b, 2b, and 3b illustrate a $\lambda^{-1/2}$ empirical convergence rate, consistent with the bound (1) we prove in the next section (Theorem 5.2). Moreover, they demonstrate that as r_b is decreased larger values of λ are required to ensure the absolute difference between the two models remains below a fixed tolerance. In all three cases, once λ is sufficiently large that the $\lambda^{-1/2}$ convergence rate can be observed, the absolute difference appears to scale like r_b^{-1} as r_b is decreased.

5 Rigorous Convergence Results

In this section we study the rigorous relationship between the Doi model (8) and Smoluchowski model (7). In Subsection 5.1 we derive a rigorous error bound on the rate of convergence of the Doi eigenvalues, $\mu_n(\lambda)$, to the Smoluchowski eigenvalues, α_n , as $\lambda \rightarrow \infty$. In Subsection 5.2 we obtain similar estimates for the convergence of the Doi eigenfunctions, ψ_n^{out} , to the Smoluchowski eigenfunctions, ϕ_n . We obtain our main result in subsection 5.3 where we use these eigenvalue and eigenfunction estimates to show the uniform convergence in space and time of the solution to the Doi model (8), $p_\lambda(r, t)$, to the solution of the Smoluchowski model (7), $\rho(r, t)$, as $\lambda \rightarrow \infty$. (With the error bound (1).)

5.1 Eigenvalue Estimates

In this subsection we derive estimates for the difference between the Doi, $\mu_n(\lambda)$, and Smoluchowski, α_n , eigenvalues. We start by proving some properties of the functions $A(\mu, \lambda)$ and $f(\mu)$ that we will find useful:

Proposition 5.1. *$A(\mu, \lambda)$ is monotone increasing. Furthermore for $\mu \leq \lambda$, A is positive.*

Proof. Positivity is trivial since \tanh is positive. Note also that $A(0, \lambda) = \tanh(\sqrt{\lambda}r_b)/\sqrt{\lambda}$. A simple computation shows that for $\mu < \lambda$

$$\frac{d}{d\mu}A(\mu; \lambda) = \frac{\tanh(\sqrt{\lambda - \mu}r_b) - r_b\sqrt{\lambda - \mu}(\operatorname{sech}^2(\sqrt{\lambda - \mu}r_b))}{2(\lambda - \mu)^{3/2}} = \frac{\sinh(2\sqrt{\lambda - \mu}r_b) - 2r_b\sqrt{\lambda - \mu}}{4\cosh^2(\sqrt{\lambda - \mu}r_b)(\lambda - \mu)^{3/2}}$$

and for $\mu > \lambda$

$$\frac{d}{d\mu}A(\mu; \lambda) = \frac{r_b\sqrt{\mu - \lambda}(\sec^2(\sqrt{\mu - \lambda}r_b)) - \tan(\sqrt{\mu - \lambda}r_b)}{2(\lambda - \mu)^{3/2}} = \frac{2r_b\sqrt{\mu - \lambda} - \sin(2\sqrt{\mu - \lambda}r_b)}{4\cos^2(\sqrt{\mu - \lambda}r_b)(\mu - \lambda)^{3/2}}.$$

The result follows since for $u \geq 0$, $\sinh(u) \geq u$ and $\sin(u) \leq u$. \square

Let the vertical asymptotes of $f(\mu)$ be denoted by β_n . They satisfy the equation

$$R\beta_n \tan(\sqrt{\beta_n}(R - r_b)) + \sqrt{\beta_n} = 0; \quad \beta_n > 0.$$

Proposition 5.2. *We have the following*

1. $0 < \alpha_1 < \beta_1 < \alpha_2 < \dots < \beta_n < \alpha_{n+1} < \dots$
2. $f'(\mu) < 0$ and $f(\mu) > 0$ on $[0, \alpha_1)$ and (β_n, α_{n+1}) for $n \geq 1$.

Proof. 1. Let $\kappa = 1 - r_b/R$ and $x = R\sqrt{\mu}$. We make the change of variable in $f(\mu)$ and obtain

$$f(\mu) \equiv \tilde{f}(x) = \frac{R(x - \tan(\kappa x))}{x^2 \tan(\kappa x) + x} = \frac{R\left(1 - \frac{\tan(\kappa x)}{x}\right)}{x \tan(\kappa x) + 1} \equiv \frac{N(x)}{D(x)}.$$

Let d_n be such that $N(d_n) = 0$ and η_n be such that $D(\eta_n) = 0$. In terms of the old variable, we have $d_n = R\sqrt{\alpha_n}$ and $\eta_n = R\sqrt{\beta_n}$. $N(x) = 0$ imply that $\tan(\kappa x) = x$ and $D(x) = 0$ imply that $\tan(\kappa x) = -\frac{1}{x}$. Note that the functions $\tan(\kappa x)$, x and $-\frac{1}{x}$ are all monotone increasing. Finally if we let $\theta_n = \frac{\pi}{2\kappa}(2n - 1)$ be the vertical asymptotes of $\tan(\kappa x)$ one easily checks that we have

$$0 < d_1 < \theta_1 < \eta_1 < \dots < d_n < \theta_n < \eta_n \dots$$

This proves 1.

2. $N > 0$ on $\bigcup_{n \geq 1} (\theta_n, d_{n+1}) \cup (0, d_1)$, and $N < 0$ on $\bigcup_{n \geq 1} (d_n, \theta_n)$. Similarly, $D > 0$ on $\bigcup_{n \geq 1} (\eta_n, \theta_{n+1}) \cup (0, \theta_1)$

and $D < 0$ on $\bigcup_{n \geq 1} (\theta_n, \eta_n)$. Thus it follows that $\tilde{f}(x) > 0$ if and only if $x \in \bigcup_{n \geq 1} (\eta_n, d_{n+1}) \cup (0, d_1)$. Next, we show that $f' < 0$. Note

$$N'(x) = \frac{R(\tan(\kappa x) - \kappa x \sec^2(\kappa x))}{x^2} = \frac{R(\sin(2\kappa x) - 2\kappa x)}{2x^2 \cos^2(\kappa x)},$$

and

$$D'(x) = \tan(\kappa x) + \kappa x \sec^2(\kappa x) = \frac{\sin(2\kappa x) + 2\kappa x}{2\cos^2(\kappa x)}.$$

Since $|\sin(\theta)| \leq |\theta|$ it follows that $N'(x) \leq 0$ and that $D'(x) \geq 0$, with equality in both only when $x = 0$. From what we have shown above, $\tilde{f}(x) > 0$ if and only if both $N(x) > 0$ and $D(x) > 0$ so that

$$f'(\mu) = \tilde{f}'(x) \cdot \frac{dx}{d\mu} = \left[\frac{D(x)N'(x) - N(x)D'(x)}{D(x)^2} \right] \cdot \frac{dx}{d\mu} < 0.$$

\square

Proposition 5.3. *The Doi eigenvalues $\mu_n(\lambda)$ satisfy for n such that $\mu_n(\lambda) \leq \lambda$*

$$0 < \mu_1(\lambda) < \alpha_1 < \beta_1 < \mu_2(\lambda) < \alpha_2 < \dots < \beta_{n-1} < \mu_n(\lambda) < \alpha_n$$

Proof. This follows from the fact that $f(\mu)$ is decreasing wherever it is positive and that $A(\mu; \lambda)$ is positive and increasing for $\mu \leq \lambda$. \square

We will also have need for the following

Proposition 5.4. *Let $\{\gamma_n\}$ denote the eigenvalues for the (positive) radially symmetric Laplacian on $[0, R)$, with zero Neumann boundary conditions on the ball of radius R . Let α_n and μ_n be as above. Then the following hold:*

1. *The $\mu_n(\lambda)$ are continuous and monotone increasing in λ for all $n \geq 1$*
2. *For all $n \geq 1$ and any fixed λ , we have that*

$$\mu_n(0) = \gamma_n = \left(\frac{(n-1)\pi}{R} \right)^2 \leq \mu_n(\lambda)$$

Remark 5.1. The proof is a straightforward application of the variational minimax principle of Poincare. We do not show it here.

Proposition 5.5. *For any $L \in \mathbb{R}_+$, define the index set $\mathcal{A}(L) = \{n | \alpha_n \leq L\}$. If we let $|\mathcal{A}(L)| \equiv \text{card}(\mathcal{A}(L))$ then given $\delta > 0$ there exists constants $C_1^*(\delta)$ and $C_2^*(\delta)$ such that for $L \geq \delta$*

$$C_1^*(\delta)\sqrt{L} \leq |\mathcal{A}(L)| \leq C_2^*(\delta)\sqrt{L} \quad (21)$$

Proof. Write $\tilde{L} = R\sqrt{L}$ and again define $\kappa = 1 - r_b/R$. Then $|\mathcal{A}(L)|$ is just the number of solutions to $\tan(\kappa x) = x$ which lie in the interval $[0, \tilde{L}]$. This number is well approximated by the number of vertical asymptotes of $\tan(\kappa x)$. It then follows that

$$\frac{\kappa\tilde{L}}{\pi} - 1 \leq |\mathcal{A}(L)| \leq \frac{\kappa\tilde{L}}{\pi} + 1$$

so that

$$\sqrt{L} \left(\frac{R - r_b}{\pi} - \frac{1}{\sqrt{L}} \right) \leq |\mathcal{A}(L)| \leq \sqrt{L} \left(\frac{R - r_b}{\pi} + \frac{1}{\sqrt{L}} \right).$$

If $L \geq \delta$ the choice $C_1^*(\delta) = \frac{R - r_b}{\pi} - \frac{1}{\sqrt{\delta}}$ and $C_2^*(\delta) = \frac{R - r_b}{\pi} + \frac{1}{\sqrt{\delta}}$ gives the proposition. \square

Remark 5.2. In practice we will choose $\delta = 4\pi^2/(R - r_b)^2$ so that $C_1^* = (R - r_b)/2\pi$.

We now give our main convergence estimate for the eigenvalues of the Doi model. The following theorem can be regarded as the heart of the subsequent computations.

Theorem 5.1. *Let $0 < \sigma_0 < \frac{1}{4}$ and define $M(\lambda) \equiv K_0\lambda^\sigma$ for $K_0 > 1$. For any fixed $\sigma \in (0, \sigma_0]$ there exists $\lambda_0 > 0$ such that for $\lambda \geq \lambda_0$, $\frac{M(\lambda)}{\lambda} \leq \frac{1}{2}$. Then for $\alpha_n \leq M(\lambda)$, $\mu_n(\lambda) \rightarrow \alpha_n$, $\mathcal{O}(\lambda^{-(\frac{1}{2}-2\sigma)})$.*

Remark 5.3. Note that in the remainder C will denote an arbitrary constant that may depend on R , r_b , and λ_0 . We will also subsequently assume $\lambda_0 > 1$.

Proof. Recall that the Doi eigenvalues $\mu_n(\lambda)$ satisfy

$$f(\mu_n(\lambda)) = A(\mu_n(\lambda), \lambda).$$

As before let $\kappa = 1 - r_b/R$ and let $x = R\sqrt{\mu}$. Recalling the definitions of $D(x)$ and $N(x)$ from Proposition 5.2, define

$$B(x; \lambda) = D(x)\tilde{A}(x, \lambda) \equiv \frac{[x \tan(\kappa x) + 1] \tanh\left(r_b \sqrt{1 - \frac{x^2}{\lambda R^2}}\right)}{\sqrt{\lambda} \sqrt{1 - \frac{x^2}{\lambda R^2}}}.$$

It follows that the rescaled Doi eigenvalues $x_n(\lambda)$ satisfy

$$N(x_n(\lambda)) = B(x_n(\lambda); \lambda).$$

For $K_0 > 1$ we choose $\lambda \geq (2K_0)^{\frac{1}{1-\sigma_0}}$ so that $\frac{M(\lambda)}{\lambda} \leq \frac{1}{2}$. Recall $f(\mu) \equiv \tilde{f}(x)$. We restrict to $\{x : \frac{x^2}{R^2} \leq M(\lambda), \tilde{f}(x) \geq 0\}$, and let $h(u) = (1 - u)^{-1/2}$. Since h is monotone it follows that

$$\frac{1}{\sqrt{\lambda} \sqrt{1 - \frac{x^2}{\lambda R^2}}} \equiv \frac{h(\frac{x^2}{R^2 \lambda})}{\sqrt{\lambda}} \leq \frac{h(\frac{1}{2})}{\sqrt{\lambda}} = \frac{\sqrt{2}}{\sqrt{\lambda}}.$$

As shown in Proposition 5.2, $\tilde{f}(x) \geq 0$ implies $-\frac{1}{x} \leq \tan(\kappa x) \leq x$ so that

$$|B(x; \lambda)| \leq \frac{[1 + x \tan(\kappa x)] \sqrt{2}}{\sqrt{\lambda}} \leq \frac{[1 + x^2] \sqrt{2}}{\sqrt{\lambda}}.$$

Write $x_n(\lambda) = d_n - \epsilon_n$. (Recall $d_n = R\sqrt{\alpha_n}$ and $\eta_n = R\sqrt{\beta_n}$.) Then

$$N(d_n - \epsilon_n) = B(x_n(\lambda); \lambda).$$

Applying the mean value theorem we get, for some $e_n \in (x_n(\lambda), d_n)$, that

$$N(d_n) - N'(e_n)\epsilon_n = B(x_n(\lambda); \lambda).$$

As $N(d_n) = 0$ and $N'(e_n) < 0$,

$$|N'(e_n)|\epsilon_n \leq \frac{[1 + x_n^2] \sqrt{2}}{\sqrt{\lambda}}$$

which gives that

$$\epsilon_n \leq \frac{\sqrt{2} [1 + x_n^2] (2e_n^2 \cos^2(\kappa e_n))}{R\sqrt{\lambda} (2\kappa e_n - \sin(2\kappa e_n))} \leq \frac{\sqrt{2} [1 + d_n^2] e_n}{\kappa R\sqrt{\lambda} \left(1 - \frac{\sin(2\kappa e_n)}{2\kappa e_n}\right)} \leq \frac{C [1 + d_n^2] d_n}{\sqrt{\lambda} \left(1 - \frac{\sin(2\kappa e_n)}{2\kappa e_n}\right)} \quad (22)$$

For any fixed $c \in (0, \kappa x_1(1))$, monotonicity of the eigenvalues implies $0 < \frac{c}{2\kappa} \leq x_1(\lambda_0) \leq x_n(\lambda) < e_n < d_n$, and therefore $c < 2\kappa e_n$. Define $l(\theta) = 1 - \frac{\sin(\theta)}{\theta}$. It follows easily that for $\theta \geq c$ there exists $0 < m < 1$ such that

$$m \leq l(\theta) \leq 1$$

Using this bound in (22), in the original unscaled variables we find that

$$R(\sqrt{\alpha_n} - \sqrt{\mu_n}) \leq \frac{CR\sqrt{\alpha_n} [1 + R^2\alpha_n]}{\sqrt{\lambda}} \quad (23)$$

which implies

$$\alpha_n - \mu_n \leq \frac{2C\alpha_n [1 + R^2\alpha_n]}{\sqrt{\lambda}}.$$

For $\alpha_n \leq M(\lambda) \equiv K_0\lambda^\sigma$, $M(\lambda) > 1$ implies

$$\alpha_n - \mu_n \leq \frac{C(M(\lambda))^2}{\sqrt{\lambda}} \equiv \frac{CK_0^2}{\lambda^{\frac{1}{2}-2\sigma}}.$$

□

Remark 5.4. Of interest is the possibility of tighter estimates here. In fact, one can show that if $f''(\mu) > 0$ wherever $f(\mu) > 0$ we actually have

$$\alpha_n - \mu_n \leq \frac{C\alpha_n}{\lambda^{\frac{1}{2}}}.$$

Theorem 5.1 and Proposition 5.4 immediately implies

Corollary 5.1. *For any fixed n , we have that $\mu_n(\lambda)$ converges monotonically to α_n as $\lambda \rightarrow \infty$.*

5.2 Eigenfunction Estimates

In this subsection we carry over the estimates for the eigenvalues obtained in the last subsection to obtain the uniform convergence in r of the eigenfunctions as $\lambda \rightarrow \infty$. Though unstated, in the remainder all theorems and lemmas include the assumptions of Theorem 5.1.

Lemma 5.1. *The (unnormalized) Doi and Smoluchowski eigenfunctions satisfy*

$$\sup_{r \in [r_b, R]} |\phi_n(r) - \psi_n^{\text{out}}(r)| = \mathcal{O}\left(\lambda^{-(\frac{1}{2} - \frac{3\sigma}{2})}\right)$$

for $\mu_n < M(\lambda) = K_0\lambda^\sigma$ as $\lambda \rightarrow \infty$.

Proof.

$$\begin{aligned} |\phi_n(r) - \psi_n^{\text{out}}(r)| &\leq \frac{1}{r} \left| \frac{\sin(\sqrt{\alpha_n}(R-r))}{R\sqrt{\alpha_n}} - \frac{\sin(\sqrt{\mu_n}(R-r))}{R\sqrt{\mu_n}} \right| + \frac{1}{r} \left| \cos(\sqrt{\mu_n}(R-r)) - \cos(\sqrt{\alpha_n}(R-r)) \right| \\ &:= I + II \end{aligned}$$

Note that

$$\begin{aligned} I &\leq \frac{1}{r_b} \left| \frac{\sin(\sqrt{\alpha_n}(R-r))}{R\sqrt{\alpha_n}} - \frac{\sin(\sqrt{\mu_n}(R-r))}{R\sqrt{\alpha_n}} \right| + \frac{1}{r_b} \left| \frac{\sin(\sqrt{\mu_n}(R-r))}{R\sqrt{\alpha_n}} - \frac{\sin(\sqrt{\mu_n}(R-r))}{R\sqrt{\mu_n}} \right| \\ &:= I_a + I_b. \end{aligned}$$

We find

$$I_a \leq \frac{1}{Rr_b\sqrt{\alpha_n}} \left| 2 \sin\left((R-r)\frac{\sqrt{\alpha_n} - \sqrt{\mu_n}}{2}\right) \cos\left((R-r)\frac{\sqrt{\alpha_n} + \sqrt{\mu_n}}{2}\right) \right| \leq \frac{(R-r_b)(\sqrt{\alpha_n} - \sqrt{\mu_n})}{Rr_b\sqrt{\alpha_n}}.$$

Similarly we have

$$I_b \leq \frac{|\sin(\sqrt{\mu_n}(R-r))|}{Rr_b} \left[\frac{1}{\sqrt{\mu_n}} - \frac{1}{\sqrt{\alpha_n}} \right] \leq \frac{(R-r_b)}{Rr_b} \left[\frac{\sqrt{\alpha_n} - \sqrt{\mu_n}}{\sqrt{\alpha_n}} \right].$$

Combining these with (23)

$$I \leq \frac{C [1 + R^2 \alpha_n]}{\sqrt{\lambda}} \leq \frac{CM(\lambda)}{\sqrt{\lambda}} = \frac{CK_0}{\lambda^{\frac{1}{2}-\sigma}}.$$

For II we have

$$\begin{aligned} II &\leq \frac{1}{r_b} \left[2 \sin \left((R-r) \frac{\sqrt{\alpha_n} - \sqrt{\mu_n}}{2} \right) \sin \left((R-r) \frac{\sqrt{\alpha_n} + \sqrt{\mu_n}}{2} \right) \right] \\ &\leq \frac{R-r_b}{r_b} (\sqrt{\alpha_n} - \sqrt{\mu_n}) \\ &\leq \frac{C(R-r_b)\sqrt{\alpha_n} [1 + R^2 \alpha_n]}{r_b \sqrt{\lambda}} \\ &\leq \frac{C(M(\lambda))^{\frac{3}{2}}}{\sqrt{\lambda}} = \frac{CK_0^{\frac{3}{2}}}{\lambda^{\frac{1}{2}-\frac{3\sigma}{2}}}. \end{aligned}$$

It follows that

$$|\phi_n(r) - \psi_n^{out}(r)| \leq \frac{CK_0}{\lambda^{\frac{1}{2}-\frac{3\sigma}{2}}} \left[\frac{1}{\lambda^{\sigma/2}} + \sqrt{K_0} \right] \leq \frac{C_1(r_b, R, K_0)}{\lambda^{\frac{1}{2}-\frac{3\sigma}{2}}} \quad (24)$$

This concludes the proof. \square

We now prove several uniform properties of the eigenfunctions we will use in the next subsection.

Lemma 5.2. 1. *There exist a λ_0 , $C_2 = C_2(r_b, R)$, such that for all $\lambda \geq \lambda_0$ and $n \in \mathbb{Z}^+$*

$$\max \left(\sup_{r \in [r_b, R]} |\psi_n^{out}(r)|, \sup_{r \in [r_b, R]} |\phi_n(r)| \right) \leq C_2. \quad (25)$$

2. *Let $b_n = \|\psi_n\|_2^{-2}$ and $a_n = \|\phi_n\|_2^{-2}$. Then there exists C_3 such that for all $\lambda \geq \lambda_0$*

$$\max \left(\sup_n \{a_n\}, \sup_n \{b_n\} \right) \leq C_3. \quad (26)$$

Proof. 1. We start by defining for $z \geq 0$, and $r_b \leq r \leq R$ the auxiliary function

$$H(z, r) := \frac{1}{r} \left[\frac{\sin(\sqrt{z}(R-r))}{R\sqrt{z}} - \cos(\sqrt{z}(R-r)) \right].$$

Note $\phi_n(r) \equiv H(\alpha_n, r)$ and $\psi_n^{out}(r) \equiv H(\mu_n, r)$. Now for $z \geq z_0 > 0$ we have that

$$\begin{aligned} |H(z, r)| &= \frac{1}{r} \left| \left[\frac{\sin(\sqrt{z}(R-r))}{R\sqrt{z}} - \cos(\sqrt{z}(R-r)) \right] \right| \\ &\leq \frac{1}{r_b} \left[\frac{1}{R\sqrt{z}} + 1 \right] \\ &\leq \frac{1}{r_b} \left[\frac{1}{R\sqrt{z_0}} + 1 \right] =: C_2(z_0). \end{aligned}$$

By Corollary 5.1 there exists λ_0 such that for $\lambda \geq \lambda_0$

$$\alpha_1 \geq \mu_1(\lambda) \geq \mu_1(\lambda_0) \geq \frac{\alpha_1}{2} > 0.$$

Note that we are using the fact that both the Doi and Smoluchowski eigenvalues can be written in non-decreasing order. Choosing $z_0 = \alpha_1/2$, proves the first part of the lemma.

2. To prove the second part start by defining

$$h(z) := \int_{r_b}^R (H(z, r))^2 r^2 dr.$$

Once again we have that $\|\psi_n^{out}\|_2^2 \equiv h(\mu_n)$ and $\|\phi_n\|_2^2 \equiv h(\alpha_n)$. *A priori* we have that $h(z) > 0$ for all $z \geq 0$. An explicit computation shows that for $z > 0$, $h(z)$ is continuous, $\lim_{z \rightarrow \infty} h(z) = (R - r_b)/2 > 0$, and $\lim_{z \rightarrow 0} h(z) = (R^3 - r_b^3)/3R^2$. With the positivity of $h(z)$ on $[0, \infty)$, these results imply that $A := \inf h(z) > 0$. It then follows that

$$a_n = \frac{1}{\|\phi_n\|_2^2} \equiv \frac{1}{h(\alpha_n)} \leq \frac{1}{A} =: C_3$$

and

$$b_n = \frac{1}{\|\psi_n\|_2^2} \leq \frac{1}{\|\psi_n^{out}\|_2^2} \equiv \frac{1}{h(\mu_n)} \leq \frac{1}{A} =: C_3.$$

This concludes the proof of the lemma. \square

These results imply that

Lemma 5.3. *There exists C_4 such that for n with $\mu_n(\lambda) \leq \alpha_n \leq M(\lambda)$*

$$|b_n - a_n| \leq \frac{C_4}{\lambda^{\frac{1}{2} - \frac{3\sigma}{2}}}.$$

Proof. We start by noting that

$$\begin{aligned} \left| \|\psi_n^{out}\|_2^2 - \|\phi_n\|_2^2 \right| &= \left| \int_{r_b}^R ((\psi_n^{out})^2 - \phi_n^2) r^2 dr \right| \\ &\leq \int_{r_b}^R |\psi_n^{out} - \phi_n| |\phi_n + \psi_n^{out}| r^2 dr \\ &\leq \frac{C_1(r_b, R, K_0)}{\lambda^{\frac{1}{2} - \frac{3\sigma}{2}}} \left[\sup_{r \in [r_b, R]} (|\psi_n^{out}| + |\phi_n|) \right] \int_{r_b}^R r^2 dr = \frac{2C_1C_2(R^3 - r_b^3)}{3\lambda^{\frac{1}{2} - \frac{\sigma}{2}}}. \end{aligned}$$

To get the last line, we have used Lemmas 5.1 and 5.2. A direct computation shows that

$$\begin{aligned} \left| \|\psi_n^{out}\|_2^2 - \|\psi_n\|_2^2 \right| &= \|\psi_n^{in}\|_2^2 = \left(\frac{\frac{1}{R\sqrt{\mu_n}} \sin(\sqrt{\mu_n}(R - r_b)) - \cos(\sqrt{\mu_n}(R - r_b))}{\sinh(r_b\sqrt{\lambda - \mu_n})} \right)^2 \int_0^{r_b} \sinh^2(r\sqrt{\lambda - \mu_n}) r^2 dr \\ &\leq \frac{C (\sinh(2r_b\sqrt{\lambda - \mu_n}) - 2r_b\sqrt{\lambda - \mu_n})}{\sqrt{\lambda - \mu_n} \sinh^2(r_b\sqrt{\lambda - \mu_n})} \leq \frac{C}{\lambda^{\frac{1}{2}}}. \end{aligned}$$

(Here we have used that $\sqrt{\lambda - \mu_n} \geq \sqrt{\lambda - M(\lambda)} \geq \sqrt{\frac{\lambda}{2}}$.) Using the preceding bounds we find, that

$$\begin{aligned} |b_n - a_n| &= \left| \frac{1}{\|\psi_n\|_2^2} - \frac{1}{\|\phi_n\|_2^2} \right| = \frac{|\|\phi_n\|_2^2 - \|\psi_n\|_2^2|}{\|\phi_n\|_2^2 \|\psi_n\|_2^2} \leq \frac{|\|\psi_n^{out}\|_2^2 - \|\psi_n\|_2^2|}{\|\psi_n\|_2^2 \|\phi_n\|_2^2} + \frac{|\|\psi_n^{out}\|_2^2 - \|\phi_n\|_2^2|}{\|\psi_n\|_2^2 \|\phi_n\|_2^2} \\ &\leq \frac{CC_3^2}{\lambda^{\frac{1}{2}}} + \frac{2C_1C_2C_3^2(R^3 - r_b^3)}{3\lambda^{\frac{1}{2} - \frac{3\sigma}{2}}} \\ &= \frac{1}{\lambda^{\frac{1}{2} - \frac{3\sigma}{2}}} \left[\frac{CC_3^2}{\lambda^{\frac{3\sigma}{2}}} + \frac{2}{3}C_1C_2C_3^2(R^3 - r_b^3) \right]. \end{aligned}$$

The choice $C_4 = CC_3^2 + 2C_1C_2C_3^2(R^3 - r_b^3)/3$ gives the lemma. \square

5.3 An Error Estimate for the Convergence of the Doi to Smoluchowski Model

We now show the uniform convergence of the Green's function of the radially symmetric Doi PDE (8) to the Green's function of the radially symmetric Smoluchowski PDE (7) model. The error bound we give shows that the convergence of the Doi model to the Smoluchowski model can not be expected to be faster than $O(\lambda^{-1/2})$ as $\lambda \rightarrow \infty$.

Theorem 5.2. *Fix $0 < \sigma_0 < \frac{1}{4}$ and let the initial condition $g(r) = \delta(r - r_0)/r^2$, where $r_0 \in (r_b, R)$. For $t \geq \delta > 0$, there exists a function $u(t)$ and λ_0 such that for all $\lambda \geq \lambda_0$ we have:*

$$\sup_{r \in [r_b, R]} |\rho(r, t) - p_\lambda(r, t)| \leq \frac{u(t)}{\lambda^{\frac{1}{2} - 2\sigma}}. \quad (27)$$

Moreover, for $t \in [\delta, \infty)$, $u(t)$ is uniformly bounded.

Proof. The main idea is to use the series representation of the solutions to both models to estimate the error. There will be a proliferation of constants which we shall repeatedly and unceremoniously denote by C . For $r \in (r_b, R)$, we begin by writing:

$$\begin{aligned} p_\lambda(r, t) - \rho(r, t) &= \sum_{\{n | \alpha_n < M(\lambda)\}} b_n \psi_n(r_0) \psi_n^{\text{out}}(r) e^{-\mu_n(\lambda)t} - a_n \psi_n(r_0) \phi_n(r) e^{-\alpha_n t} \\ &\quad + \sum_{\{n | \alpha_n \geq M(\lambda)\}} b_n \psi_n(r_0) \psi_n^{\text{out}}(r) e^{-\mu_n(\lambda)t} - a_n \psi_n(r_0) \phi_n(r) e^{-\alpha_n t} \\ &:= I + II. \end{aligned}$$

We deal with the finitely indexed sum, I , first. Define the index set $\mathcal{A}_\lambda = \{n \mid \alpha_n < M(\lambda)\}$. From now on, for simplicity of presentation, we write ψ_n for ψ_n^{out} . Let $I = I_a + I_b + I_c + I_d$, where

$$\begin{aligned} I_a &= \sum_{\mathcal{A}_\lambda} b_n (\psi_n(r_0) - \phi_n(r_0)) \psi_n(r) e^{-\mu_n(\lambda)t}, & I_b &= \sum_{\mathcal{A}_\lambda} b_n \phi_n(r_0) (\psi_n(r) - \phi_n(r)) e^{-\mu_n(\lambda)t}, \\ I_c &= \sum_{\mathcal{A}_\lambda} (b_n - a_n) \phi_n(r_0) \phi_n(r) e^{-\mu_n(\lambda)t}, & I_d &= \sum_{\mathcal{A}_\lambda} a_n \phi_n(r_0) \phi_n(r) (e^{-\mu_n(\lambda)t} - e^{-\alpha_n t}). \end{aligned}$$

Recalling that γ_n denotes the n th eigenvalue of the radially symmetric Laplacian on $[0, R]$ with a zero Neumann boundary condition at R (see Proposition 5.4), we find

$$|I_a| \leq \sum_{\mathcal{A}_\lambda} |b_n| |\psi_n(r)| |\psi_n(r_0) - \phi_n(r_0)| e^{-\mu_n t} \leq \frac{C}{\lambda^{\frac{1}{2} - \frac{3\sigma}{2}}} \sum_{n=1}^{\infty} e^{-\gamma_n t}.$$

Here we have applied Proposition 5.4, Lemma 5.1, and Lemma 5.2 (in particular (24), (25), and (26)). The same argument shows

$$|I_b| \leq \sum_{\mathcal{A}_\lambda} |b_n| |\psi_n(r) - \phi_n(r)| |\phi_n(r_0)| e^{-\mu_n t} \leq \frac{C}{\lambda^{\frac{1}{2} - \frac{3\sigma}{2}}} \sum_{n=1}^{\infty} e^{-\gamma_n t},$$

and using Lemma 5.3 too we find

$$|I_c| \leq \sum_{\mathcal{A}_\lambda} |b_n - a_n| |\phi_n(r_0)| |\phi_n(r)| e^{-\mu_n t} \leq \frac{C}{\lambda^{\frac{1}{2} - \frac{3\sigma}{2}}} \sum_{n=1}^{\infty} e^{-\gamma_n t}.$$

Finally, we have that

$$|I_d| \leq \sum_{\mathcal{A}_\lambda} |a_n| |\phi_n(r)| |\phi_n(r_0)| \left| 1 - e^{-(\alpha_n - \mu_n)t} \right| e^{-\mu_n t}.$$

For $s \geq 0$, $1 - e^{-s} \leq |s|$ so that, using the same lemmas as before and Theorem 5.1,

$$|I_d| \leq C \sum_{\mathcal{A}_\lambda} e^{-\mu_n t} |\alpha_n - \mu_n| t \leq \frac{C}{\lambda^{\frac{1}{2}-2\sigma}} \sum_{n=1}^{\infty} t e^{-\mu_n t}.$$

We now bound the tail of the series, II . First define the index set $\mathcal{B}_\lambda = \{n \mid \alpha_n \geq M(\lambda)\}$. We now specify the choice $K_0 > 4\pi^2/(R-r_b)^2$ which guarantees that $K_0\lambda^\sigma > 4\pi^2/(R-r_b)^2$ (see Remark 5.2 after the proof of Proposition 5.5). Using the uniform bounds on ψ_n , ϕ_n , a_n , and b_n and Proposition 5.5 we find

$$|II| \leq C_1 \sum_{n \geq C_1^* \sqrt{K_0} \lambda^{\frac{\sigma}{2}}} e^{-\mu_n t} + C_2 \sum_{n \geq C_1^* \sqrt{K_0} \lambda^{\frac{\sigma}{2}}} e^{-\alpha_n t} \leq C \sum_{n \geq \lambda^{\frac{\sigma}{2}}} e^{-\gamma_n t}.$$

We thus obtain the error estimate that

$$|\rho(r, t) - p_\lambda(r, t)| \leq C \left[\frac{1}{\lambda^{\frac{1}{2}-\frac{3\sigma}{2}}} \sum_{n=1}^{\infty} e^{-\gamma_n t} + \frac{1}{\lambda^{\frac{1}{2}-2\sigma}} \sum_{n=1}^{\infty} t e^{-\mu_n t} + \sum_{n \geq \lambda^{\frac{\sigma}{2}}} e^{-\gamma_n t} \right]. \quad (28)$$

We estimate the terms in (28) one at a time. First

$$\sum_{n=1}^{\infty} e^{-\gamma_n t} = \sum_{n=0}^{\infty} \exp \left[-\frac{n^2 t \pi^2}{R^2} \right] \leq 1 + \int_0^{\infty} \exp \left[-\frac{x^2 t \pi^2}{R^2} \right] dx = 1 + \frac{R}{\sqrt{4\pi t}},$$

while

$$\begin{aligned} \sum_{n=1}^{\infty} t e^{-\mu_n t} &\leq t e^{-\mu_1(\lambda)t} + \sum_{n=2}^{\infty} t e^{-\gamma_n t} \\ &\leq t e^{-\mu_1(\lambda_0)t} + \sum_{n=1}^{\infty} t \exp \left[-\frac{n^2 t \pi^2}{R^2} \right] \\ &\leq \frac{1}{e\mu_1(\lambda_0)} + \frac{R^2}{e\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \leq \bar{C}. \end{aligned}$$

Finally, we bound the third term in (28):

$$\begin{aligned} \sum_{n \geq \lambda^{\frac{\sigma}{2}}} e^{-\gamma_n t} &= \sum_{n \geq \lambda^{\frac{\sigma}{2}-1}} \exp \left[-\frac{n^2 t \pi^2}{R^2} \right] \\ &\leq \int_{\lambda^{\frac{\sigma}{2}-2}}^{\infty} \exp \left[-\frac{x^2 t \pi^2}{R^2} \right] dx \\ &\leq \frac{R}{\sqrt{4\pi t}} \operatorname{erfc} \left(\frac{(\lambda^{\sigma/2}-2)\sqrt{t}\pi}{R} \right) \\ &\leq \frac{\hat{C}R}{\sqrt{4\pi t}} e^{-\tilde{C}\lambda^\sigma t}. \end{aligned}$$

Combining the preceding estimates we have

$$\begin{aligned} |\rho(r, t) - p_\lambda(r, t)| &\leq \frac{C}{\lambda^{\frac{1}{2}-2\sigma}} \left[\frac{1}{\lambda^{\sigma/2}} \left(1 + \frac{R}{\sqrt{4\pi t}} \right) + \bar{C} + \hat{C}\lambda^{\frac{1}{2}-2\sigma} \frac{R}{\sqrt{4\pi t}} e^{-\tilde{C}\lambda^\sigma t} \right] \\ &\leq \frac{C}{\lambda^{\frac{1}{2}-2\sigma}} \left[\frac{1}{\sqrt{t}} \left(1 + \frac{C(\sigma)}{t^{\frac{1}{2\sigma}-2}} \right) + 1 \right]. \end{aligned}$$

Here we absorbed the maximum of the many constants into C and

$$C(\sigma) \equiv \left(\frac{1}{\bar{C}_e} \left[\frac{1}{2\sigma} - 2 \right] \right)^{\frac{1}{2\sigma} - 2}.$$

Let

$$u(t) := C \left[\frac{1}{\sqrt{t}} \left(1 + \frac{C(\sigma)}{t^{\frac{1}{2\sigma} - 2}} \right) + 1 \right].$$

For $t \geq \delta > 0$ we see that $u(t)$ is uniformly bounded, concluding the proof. \square

Remark 5.5. Note that even for $t \geq \delta > 0$, $u(t) \rightarrow \infty$ as $\sigma \rightarrow 0$ because $u(t)$ blows up like $\left(\frac{1}{\sqrt{\delta\sigma}} \right)^{\frac{1}{\sigma}}$.

6 Conclusion

We have shown for the special case of two molecules that may undergo the annihilation reaction, $A + B \rightarrow \emptyset$, with one of the two molecules stationary, the solution to the Doi model (29) converges to the solution of the Smoluchowski model (30) as $\lambda \rightarrow \infty$. A rigorous asymptotic convergence rate that is $O(\lambda^{-\frac{1}{2} + \epsilon})$, for all fixed $\epsilon > 0$, was proven for the maximum difference between the two models over all $r \in (r_b, R)$ and $t \in (\delta, \infty)$ (for any fixed $\delta > 0$). Numerical evaluation of the exact eigenfunction expansions, binding time distributions, and mean binding times illustrated this convergence rate, and demonstrated that for sufficiently large fixed values of λ the difference between the two models scaled like r_b^{-1} as r_b was decreased. For biologically relevant values of r_b , such as the reaction-radius for a protein diffusing to a fixed DNA binding site, it was found that λ should be chosen at least as large as 10^{11}s^{-1} for the mean binding time in the two models to differ by less than 1%.

There are a number of extensions of the current work that would aid in clarifying the rigorous relationship between the Smoluchowski and Doi models. Foremost would be the study of more detailed, biologically realistic, models in which multiple diffusing and reacting chemical species are present. Such models require the introduction of unbinding reactions, $C \rightarrow A + B$, which in the Smoluchowski model require the use of unbinding radii (a separation, greater than r_b , at which to place the newly created molecules to avoid their immediate rebinding). As numerical methods to solve the Doi and Smoluchowski models have been used to study biological systems, understanding how parameters in the Doi model should be chosen so as to accurately approximate the Smoluchowski model would greatly aid in comparing predictions by these different approaches.

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A Mean Binding Time

Let $\mathbb{E}[T_{\text{Doi}}]$ denote the mean time at which the two molecules in the Doi model (8) first react when initially separated by r_0 . $\mathbb{E}[T_{\text{Doi}}]$ can be shown to satisfy [15, 39]

$$\Delta_{r_0} \mathbb{E}[T_{\text{Doi}}](r_0) - \hat{\lambda} \mathbf{1}_{\{r < r_b\}}(r) \mathbb{E}[T_{\text{Doi}}](r_0) = -\frac{1}{D}, \quad 0 \leq r_0 < R, \quad (29)$$

with the boundary condition,

$$\frac{\partial \mathbb{E}[T_{\text{Doi}}]}{\partial r_0}(R) = 0.$$

(Here $\hat{\lambda} = \lambda/D$.) The solution to (29) is given by (17).

The mean time, $\mathbb{E}[T_{\text{Smol}}](r_0)$, at which the two molecules in the Smoluchowski model (7) first react when initially separated by r_0 can be shown to satisfy [15, 39]

$$\Delta_{r_0} \mathbb{E}[T_{\text{Smol}}](r_0) = -\frac{1}{D}, \quad r_b < r_0 < R, \quad (30)$$

with the boundary conditions,

$$\mathbb{E}[T_{\text{Smol}}](r_b) = 0, \quad \frac{\partial \mathbb{E}[T_{\text{Smol}}]}{\partial r_0}(R) = 0.$$

The solution to (30) is given by (18).

B Discrete Space and Time Points

The spatial evaluation points, r_i , are generated in MATLAB by

```
r1 = rb + rb*[5e-6 1e-5 5e-5 1e-4 5e-4 1e-3 5e-3]';
r = [r1; (.01:.01:1)' * (R-rb) + rb];
```

Listing 1: r_i points

The time evaluation points, t_j , are generated in MATLAB by

```
t = [1e-5 1e-4 1e-3 .01:.01:100 101:1:200 200:10:1000 1200:200:10000]';
```

Listing 2: t_j points

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